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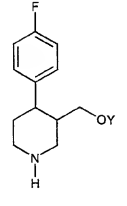

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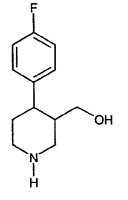

(2)

(57) Abstract: A process for manufacturing a compound of structure (1) where Y is substituted phenyl, especially 3,4-methylenedioxy-phenyl, or OY is a sulphonate leaving group; comprises coupling a compound of formula (2) to a phenolic compound such as sesamol or a sulphonic acid using a Mitsunobu reaction.

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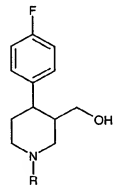
NOVEL PROCESS

The present invention relates to a new process for manufacturing pharmaceutically active compounds and intermediates therefor.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-) *trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-phenoxymethyl)-piperidine. This compound is used in therapy as the hydrochloride salt to treat inter alia depression, obsessive compulsive disorder (OCD) and panic.

This invention aims to overcome disadvantages in the existing processes for preparation of such compounds and so to provide alternative processes for their manufacture.

Previously published processes to paroxetine utilise as a key intermediate the carbinol (A)



(A)

in which the piperidine nitrogen is protected by a group R, usually an alkyl (typically methyl) group. None of these processes utilise an N-unsubstituted piperidine (i.e. R = H) as found in paroxetine itself. The N-substituted piperidine must therefore be coupled with sesamol to make an N-substituted paroxetine analogue which is converted to paroxetine by removal of the nitrogen protecting group, typically in two chemical steps (e.g. US-A-4,007,196). In these processes the piperidine carbinol must be prepared with the nitrogen

suitably protected either by means of a discrete alkylation step (e.g. EP-A-0219934 and EP-A-0300617) or by using more highly functionalised and hence more expensive reagents (e.g. EP-A-0223334) during the early synthetic stages.

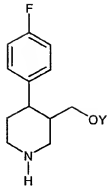
Patil and Viswanathan in Indian Drugs 1998, volume 35, pages 686-692 disclose a small scale procedure for the direct conversion of (-)-trans-4-(4'-fluorophenyl)-3-hydroxy-methylpiperidine to paroxetine and other phenolic ether derivatives by condensation with a phenolic component at elevated temperature in the presence of dicyclohexylcarbodiimide, without solvent. However, the very high temperatures required (160-180°C) are hazardous and generate unacceptable levels of thermal degradation products, rendering this process unsuitable for large scale manufacture.

Engelsoft and Hansen in Acta Chemica Scandinavia 1996, volume 50 pages 164-169 make reference to the conversion of 4-(4'-fluorophenyl)-3-hydroxymethyl-N-methyl piperidine to N-methyl paroxetine by a 'Mitsunobu' procedure. However, no experimental details are given.

It is clear that processes involving an N-protected piperidine carbinol are inefficient as they require additional chemical transformations for the removal of the N-protecting group which add to the cost of manufacture.

The present invention is based on the surprising discovery that Mitsunobu-type procedures can be used for the large scale manufacture of paroxetine by an inexpensive and efficient process involving very mild conditions of temperature and pH, and consequently reduced side reactions such as methylenedioxy bridge opening.

In one aspect, the present invention provides a process for manufacturing a compound of structure (1)



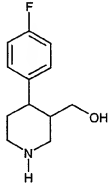
(1)

where

Y is substituted phenyl, especially 3,4-methylenedioxy-phenyl, or

OY is a sulphonate leaving group;

in which a compound of formula (2)

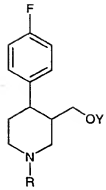


(2)

is coupled to a phenolic compound, such as sesamol, or a sulphonic acid, such as methanesulfonic acid using a redox coupling reaction, such as a Mitsunobu procedure.

Under some conditions it may be desirable to retain protection of the N atom until after completion of the coupling reaction.

Accordingly in another aspect the present invention provides a process for manufacturing a compound of structure (3)



(3)

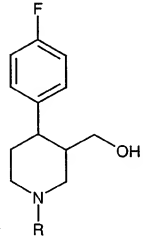
where

R is a protecting group,

Y is substituted phenyl, especially 3,4-methylenedioxy-phenyl, or

OY is a sulphonate leaving group;

in which a compound of structure (4)

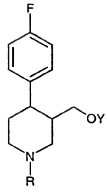


(4)

is coupled to a phenolic compound such as sesamol or a sulphonic acid using a redox coupling reaction, such as a Mitsunobu reaction.

The group R may be for example, an optionally substituted alkyl, aralkyl, aryl, acyl, alkoxycarbonyl, arylalkoxycarbonyl or aryloxycarbonyl group.

In a further aspect the present invention provides a process for manufacturing a compound of structure (3)



(3)

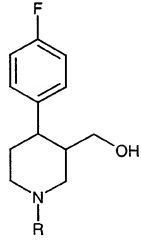
where

R is a protecting group other than a methyl group,

Y is substituted phenyl, especially 3,4-methylenedioxy-phenyl, or

OY is a sulphonate leaving group;

in which a compound of structure (4)



(4)

is coupled to a phenolic compound such as sesamol or a sulphonic acid using a redox coupling reaction, such as a Mitsunobu reaction.

The phenolic compound may be optionally substituted by one or more groups such as halogen or alkyl or alkoxy, or by two substituents linked to form a fused ring. For example, an especially suitable compound is sesamol (3,4-methylenedioxyphenol), as used in the preparation of paroxetine.

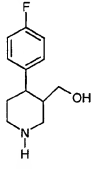
An advantage of this process is that the phenolic compound may be reacted directly, without the need to form active derivatives, such as metal salts or aryl halides.

The present invention may also be used to form intermediates where OY is a sulphonate leaving group, by reaction of a carbinol of structure (2) with a sulphonic acid. Such intermediates may be used to couple with substituted phenols such as sesamol. Suitable sulphonic acids include benzenesulphonic acid, 4-toluene-(or other substituted benzene)-sulphonic acid, methane- or trifluoromethanesulphonic acid.

The reaction of the present invention is carried out by means of a redox-coupling agent, for example, diethylazodicarboxylate with triphenylphosphine, in the presence of a solvent, for example tetrahydrofuran.

In a preferred embodiment of the present invention an unprotected piperidine carbinol of structure (2) is converted efficiently to paroxetine of structure (5) by etherification with sesamol in a single step.

When the carbinol (2) is (-)-trans-4-(4'-fluorophenyl)-3-hydroxymethylpiperidine, which may be prepared according to the procedure described in US 5258517, the process of the invention gives paroxetine.



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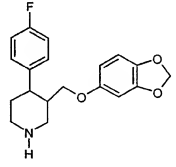


(5)

The same procedure is applicable to N-protected arylpiperidine carbinols, resulting in the preparation of N-substituted paroxetine, and although not the preferred aspect, this also forms part of this invention.

The redox couple may be any of those known in the art as suitable for this type of coupling. Preferably the reducing agent is a phosphine. For example the phosphine may be selected form trialkylphosphine, triphenylphosphine, tris(3-chlorophenyl)phosphine, phenoxydiphenylphosphine, diphenoxyphenylphosphine, tris(4-methoxyphenyl)phosphine or a polymer-bound phosphine, for example polymer-bound triphenylphosphine. Other reducing agents have been described in the literature for this type of transformation, and are included in this invention, for example reagents based on other group V elements such as arsine and stibine.

The oxidising agent preferably is selected from a dialkylazodicarboxylate, a dialkylazodicarboxamide or a polymer bound methylazodicarboxylate (which is described in Journal American Chemical Society 1989,111, p3973-3976). Preferably the redox couple is diethylazodicarboxylate or diisopropylazodicarboxylate with triphenylphosphine.

The solvent may be selected from ethers, such as diethylether, diisopropylether, tert-butylmethyl ether, or tetrahydrofuran, from chlorinated solvents such as dichloromethane, from polar aprotic solvents such as dimethylformamide, or from hydrocarbons such as toluene. Alternatively a mixture of solvents may be used. Preferably the solvent is tetrahydrofuran or dichloromethane, or a mixture of the two.

The reaction may carried out under an inert atmosphere at a temperature in the range -20 to 100°C, preferably in the range 0 to 40°C and more preferably at 15 to 30°C. Preferably the molar ratio of carbinol (2) or (4) to phenolic compound is between 1:1 and 1:1.2, more preferably between 1:1 and 1:1.1, and the molar ratio of carbinol (2) or (4) to the redox couple is between 1:1 and 1:2, more preferably between 1:1 and 1:1.5.

In a preferred embodiment of this invention diethylazodicarboxylate or diisopropylazodicarboxylate is added to a solution of the carbinol, triphenylphosphine and sesamol in tetrahydrofuran or dichloromethane at 20-30°C and the reaction mixture stirred until completion of the reaction. Paroxetine may then be isolated by separation from the by-products of the reaction, for example by extraction as an acid salt followed by crystallisation, for example as an acctate or hydrochloride, or by chromatography.

Another method for the removal of by-products of the reaction is by crystallisation from a suitable solvent. For example, at the end of a reaction, tetrahydrofuran may be replaced by toluene, and a triphenylphosphine oxide/diisopropoxycarboxy hydrazine complex is isolated from the reaction mixture by crystallisation. The residual liquors may then be washed with a dilute aqueous alkaline solution to remove acidic impurities, including sesamol, and the paroxetine extracted as an acidic salt, for example the acetate, by treatment with aqueous acid solution. Crystalline or non-crystalline paroxetine salts may be isolated from the aqueous extract by evaporation, or may be crystallised by addition of a miscible solvent such as propan-2-ol. Alternatively, a strong acid such as hydrochloric acid and an optional co-solvent such as propan-2-ol, may be added and the paroxetine isolated as a strong acid salt, for example paroxetine hydrochloride hemihydrate.

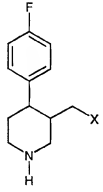
In an alternative embodiment of the process, the by-products are removed by complexation with an inorganic salt, for example anhydrous magnesium chloride. In this process an inorganic salt is added, for example as a powder and the reaction mixture stirred and heated to allow for complexation. The inorganic salt is then removed by filtration. The process may be repeated, if necessary, to remove traces of the oxidised reductant.

The processes of this invention are particularly suitable for large scale manufacture because of their efficiency and ease of operation. The product of the processes may be purified by crystallisation as an acid salt, for example the acetate, maleate, methanesulfonate, and hydrochloride salts, particularly the hemihydrate and anhydrate forms of the hydrochloride salt. Hence, after separation of by-products, the free base or salt form of paroxetine is treated with hydrogen chloride or other acid in a suitable solvent which may, for example, be a hydrocarbon such as toluene, alcohol such as ethanol or propan-2-ol, ether such as tetrahydrofuran or diisopropylether, alkyl ester such as ethyl acetate, or ketone such as acetone, butanone, or isobutylmethylketone, or a mixture of any of these solvents. The preferred solvents are toluene or propan-2-ol.

As mentioned previously, in addition to coupling with phenolic compounds, an alternative aspect of this invention employs processes based on the use of a redox couple to form

activated derivatives of structure (1) or (3) where a OY is a sulfonate group, which may themselves be used in coupling reactions.

In a related process, compounds of structure (6) or (7)



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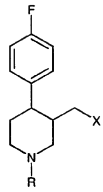


(7)

where X is a halogen atom, and R is as previously described, may be prepared as further activated derivatives of compounds of structure (2) and (4).

For example, the compound of structure (6) where X is a chlorine atom may be manufactured by the action of a chloride source, such as carbon tetrachloride, and triphenylphosphine on a carbinol of structure (2).

Intermediates of structure (3) where a OY is a sulfonate group and intermediates of structure (7) may be coupled with sesamol derivatives to form paroxetine by known methods, for example as described in US-A-4,007,196.

Intermediates of structure (1) where a OY is a sulfonate group and intermediates of structure (6) are novel, and form part of this invention. These novel intermediates may also be coupled with sesamol derivatives to form paroxetine.

Compounds of structure (2) and (4) may be prepared using procedures described in EP-A-0223334.

The process of this invention may be used to manufacture active compounds described in US-A-3912743 and US-A-4007196, and preferably to manufacture paroxetine, the compound of structure (1) in which Y is 3,4-methylenedioxy-phenyl.

Paroxetine is the (-)-*trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-phenoxymethyl)-piperidine. Following the procedure of EP-0 152 273, optical resolution may be carried out prior to coupling with the phenol. Alternatively, resolution may be carried out at other stages using conventional procedures.

Paroxetine is preferably obtained as or converted to the hydrochloride salt and most preferably the hemihydrate of that salt, as described in EP-A-0223403. The present invention includes within its scope the compound paroxetine, particularly paroxetine hydrochloride, especially as the hemihydrate, when obtained via any aspect of this invention, and any novel intermediates resulting from the described procedures.

Paroxetine obtained using this invention may be formulated for therapy in the dosage forms described in EP-A-0223403 or WO96/24595, either as solid formulations or as solutions for oral or parenteral use.

Therapeutic uses of paroxetine, especially paroxetine hydrochloride, obtained using this invention include treatment of: alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the Disorders".

Accordingly, the present invention also provides:

a pharmaceutical composition for treatment or prophylaxis of the Disorders comprising paroxetine or paroxetine hydrochloride obtained using the process of this invention and a pharmaceutically acceptable carrier,

the use of paroxetine or paroxetine hydrochloride obtained using the process of this invention to manufacture a medicament for the treatment or prophylaxis of the Disorders; and

a method of treating the Disorders which comprises administering an effective or prophylactic amount of paroxetine or paroxetine hydrochloride obtained using the process of this invention to a person suffering from one or more of the disorders.

This invention is illustrated by the following Examples.

Example 1

Diethylazodicarboxylate (0.09 ml) was added to a solution of trans-4-(4'-fluorophenyl)-3-hydroxymethylpiperidine (112 mg), triphenylphosphine (140 mg) and sesamol (74 mg) in tetrahydrofuran (5 ml) under argon. The resultant orange solution was stirred for 6 hours at room temperature. The solvent was removed by evaporation to give an oil. trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)piperidine was isolated by chromatography on silica gel (95:5 methanol:triethylamine as eluant).

Example 2

Diethylazodicarboxylate (0.54 ml) was added to a solution of trans-4-(4'-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine (1.00 g), triphenylphosphine (0.891 g) and sesamol (0.467 g) in tetrahydrofuran (10 ml) under argon and the reaction mixture was stirred for 20 hours at room temperature. The solvent was removed by evaporation to give an oil. The product, trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)-1-methylpiperidine, was isolated by chromatography on silica gel (20:1:1 dichloromethane:methanol:triethylamine as eluant).

Example 3

Diisopropylazodicarboxylate (0.50 ml) was added to a solution of trans-4-(4'-fluorophenyl)-3-hydroxymethyl piperidine (0.50 g), triphenylphosphine (0.65 g) and sesamol (0.35g) in tetrahydrofuran (10 ml) under argon. The resulting orange solution was stirred for hours at 21-22°C for 44 hours. The solvent was removed by evaporation to give trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)piperidine as a crude oil (2.13g).

Example 4

Diethylazodicarboxylate (0.09 ml) was added to a solution of trans-4-(4'-fluorophenyl)-3-hydroxymethylpiperidine (118 mg), tributylphosphine (0.15 ml) and sesamol (75 mg) in tetrahydrofuran (5 ml) under argon. The resulting orange solution was stirred for 6 hours at room temperature then evaporated under reduced pressure to trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)piperidine as a crude brown oil (0.523 g).

Example 5

A solution of trans-4-(4'-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine (1.00g), triphenylphosphine (1.50 g) in carbon tetrachloride (5 ml) and tetrahydrofuran (10 ml) was stirred vigorously at room temperature for 1 hour under argon. The reaction mixture was heated at reflux for 4 hours, then the reaction mixture was cooled, filtered, and the filtrate evaporated to give trans-4-(4'-fluorophenyl)-3-chloromethyl-1-methyl-piperidine. The product was subsequently purified by silica gel chromatography.

Example 6

Triethylamine (0.65 ml) was added to a solution of diethylazodicarboxylate (0.65 ml), trans-4-(4'-fluorophenyl)-3-hydroxymethylpiperidine (0.50 g), triphenylphosphine (0.73 g), and methanesulfonic acid (0.55 ml) in tetrahydrofuran (5 ml) under argon. The reaction mixture was stirred at 21-22°C for approximately 70 hours then heated at reflux for a further 4 hours. Aqueous sodium hydroxide was added (1ml) and the reaction mixture stirred overnight at room temperature. Tetrahydrofuran (5ml) was added and

triphenylphosphine oxide removed by filtration. The filtrate was evaporated to give trans-4-(4'-fluorophenyl)-3-methanesulfonylmethyl piperidine as an orange oil.

Example 7

Diisopropylazodicarboxylate (1.90 ml) was added to a solution of trans-4-(4'-fluorophenyl)-3-hydroxymethylpiperidine (2.02 g), triphenylphosphine (2.53 g) and sesamol (1.34 mg) in tetrahydrofuran (15 ml) under argon. The resulting orange solution was stirred for 19 hours at 21-22°C. Toluene 50 (ml) was added and the solution concentrated under reduced pressure to one third the original volume. Toluene (50 ml) was added and the solution concentrated to one third the original volume. The dark solution was left at room temperature for 3 hours. The solution was evaporated to a viscous oil which crystallised on standing at 21-22°C for 24 hours. The crystalline triphenylphosphine oxide-diisopropylhydrazinedicarboxylate complex was suspended in toluene (5 ml) and filtered off (0.87 g). Evaporation of the filtrate gave crude trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)piperidine as an oil, which was dissolved in ethyl acetate (100 ml) and washed with 2N aqueous sodium hydroxide (50 ml), then shaken with aqueous acetic acid (50 ml, 30% v/v acetic acid). The aqueous extract was evaporated to an oil and propan-2-ol (50 ml) added. The solution was re-evaporated to give substantially pure trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)piperidine acetate.

Example 8

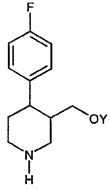
Di-tert-butylazodicarboxylate (0.230 g) was added to a solution of trans-4-(4'-fluorophenyl)-3-hydroxymethyl piperidine (0.21 g), triphenylphosphine (0.25g) and sesamol (0.15 g) in dichloromethane (8 ml) under argon. The resulting yellow solution was stirred for 19 hours at 21-22°C, then the solvent was removed by evaporation to give trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)piperidine as a crude oil.

Example 9

Diisopropylazodicarboxylate (0.4 ml) was added to a rapidly stirred suspension of trans-4-(4'-fluorophenyl)-3-hydroxymethylpiperidine (0.58 g), polymer bound triphenylphosphine (2g, approx 3 mmol/g) and sesamol (0.38 g) in tetrahydrofuran (10 ml) under argon. The suspension was stirred at room temperature for 24 hours then the polymer was removed by filtration through celite. The polymer was washed with toluene (30 ml) and the combined filtrates were evaporated to give trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)piperidine as a crude oil.

CLAIMS

1. A process for manufacturing a compound of structure (1)



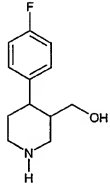
(1)

where

Y is substituted phenyl, especially 3,4-methylenedioxy-phenyl, or

OY is a sulphonate leaving group;

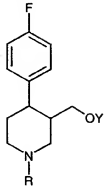
in which a compound of formula (2)



(2)

is coupled to a phenolic compound such as sesamol or a sulphonic acid using a Mitsunobu reaction.

2. A process for manufacturing a compound of structure (3)



(3)

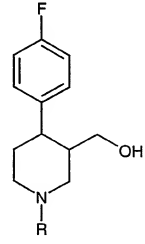
where

R is a protecting group,

Y is substituted phenyl, especially 3,4-methylenedioxy-phenyl, or

OY is a sulphonate leaving group;

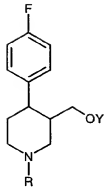
in which a compound of structure (4)



(4)

is coupled to a phenolic compound such as sesamol or a sulphonic acid using a Mitsunobu reaction.

3. A process for manufacturing a compound of structure (3)



(3)

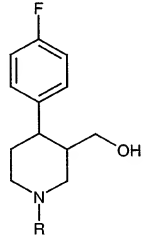
where

R is a protecting group other than a methyl group,

Y is substituted phenyl, especially 3,4-methylenedioxy-phenyl, or

OY is a sulphonate leaving group;

in which a compound of structure (4)



(4)

is coupled to a phenolic compound such as sesamol or a sulphonic acid using a Mitsunobu reaction.

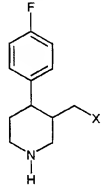
4. A process according to claim 2 or 3 in which R is an optionally substituted alkyl, aralkyl, aryl, acyl, alkoxycarbonyl, arylalkoxycarbonyl or aryloxycarbonyl group.

5. A process according to any one of claims 1 to 4 in which the coupling reagents are triphenyl phosphine/diC_{1-4}alkyl azodicarboxylate.

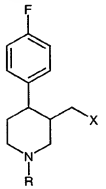
6. A compound of structure (1) where R is hydrogen and Y is 3,4-methylenedioxy-phenyl whenever obtained by a process according to any one of claims 1 to 5.

7. A compound according to claim 6, in the form of a hydrochloride salt.

8. A process for manufacturing a compound of structure (6) or (7)



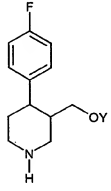
(6)



(7)

where X is a halogen atom by the action of a chloride source, such as carbon tetrachloride, and triphenylphosphine on a carbinol of structure (2) or (4).

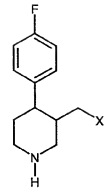
9. A compound of structure (1)



(1)

in which Y is a sulphonate leaving group.

10. A compound of structure (6)



(6)

in which X is a halogen atom.

11. A compound of structure (1) where R is hydrogen and Y is 3,4-methylenedioxy-phenyl whenever obtained by reacting a compound of structure (1) or (3) in which Y is a sulphonate leaving group, obtained by the process of claim 1, or a compound of structure (6) or (7) in which X is a halogen, obtained by the process of claim 10, with sesamol, and if necessary deprotecting.

12. A pharmaceutical composition for treatment or prophylaxis of the Disorders comprising a compound as claimed in claim 6 or 11 and a pharmaceutically acceptable carrier.

13. A method of treating the Disorders which comprises administering an effective or prophylactic amount of a compound as claimed in claim 6 or 11 to a person suffering from one or more of the disorders.